The contents of the Summary and Conclusion have been widely quoted in several publications listed in pages 322 to 343. The Editorial by Hutchison (Bull N Y Acad Med 44: 1471-1475, 1968) is one of a few that has discussed the limitations of the epidemiologic approach. The article is reproduced below.

THE NATURE OF EPIDEMIOLOGIC EVIDENCE: SMOKING AND HEALTH*

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THE SURGEON GENERAL'S REPORT

In 1964 the Advisory Committee to the Surgeon General of the Public Health Service identified a number of disease categories for which the committee was willing to state that a causal association with cigarette smoking had been established.** These were all diseases of the respiratory apparatus, including cancers of the lip, larynx, bronchus, and lung, plus one nonmalignant condition, chronic bronchitis. No cardiovascular diseases were so designated.

A second group of disease categories was identified as associated with cigarette smoking, but a causal relationship was not established. In this group were included arteriosclerotic heart disease and a category referred to as noncoronary cardiovascular disease. The noncoronary category includes endocarditis, hypertensive heart disease, and certain

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**Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, U.S. Department of Health, Education, and Welfare, Public Health Service. Washington, D.C., Govt. Print. Office, 1964.

residue rubrics of other heart and circulatory disease. In addition to these cardiovascular categories the associated group included cancers of the oral cavity, esophagus, and bladder, and the benign conditions emphysema, gastric ulcer, and cirrhosis.

The judgment relative to coronary disease is somewhat stronger than that relative to other conditions where a causal conclusion was not possible. The committee felt that a prudent course of action with respect to coronary disease should be based on a presumption of a causal association. Countermeasures should not be postponed while further refinement of the evidence is awaited. Subsequent data add strength to these conclusions.

Cause-Effect Concept

The concept of cause that is appropriate to discussions of the relation of smoking to illness should be considered here.

I should like to distinguish two concepts which I shall call the pragmatic concept and the elaborated theory concept. Under the pragmatic concept a cause-effect relation exists when *deliberate manipulation* of a series of preliminary alternatives is followed by a *statistically predictable variation* in a second series of alternatives. The preliminary manipulation is referred to as the cause, and the outcome in the second series is referred to as the effect. In the present discussion a pragmatic cause-effect would be proved if an investigator were to manipulate the smoking habits of a group and if the predicted incidence of disease was to follow. It should be noted that this concept does not involve either a necessary or sufficient relation. To say that smoking causes coronary disease permits the possibility that coronary disease occurs in some frequency in the absence of smoking. It also permits the possibility that some smokers, or even most smokers, will not develop coronary disease. This concept says nothing about the mechanism of the causal association. Finally the concept is of direct significance for public health action, since it indicates that a certain manipulation will improve health in some measure.

Under the elaborated theory concept a cause-effect relation is established by demonstrating that the relation is a consequence of laws of basic science. The emphasis is on mechanism. The relation must generally be stated in much more refined terms than "smoking" and "coronary disease." For example, it may be concluded that nicotine stimu-

lates or paralyzes certain ganglia with a consequent alteration in pulse rate. This alteration may be inconsequential in normal hearts but may set off a further chain of events in hearts with previously damaged coronary arteries. The ultimate conclusion will be that smoking is followed by coronary heart disease under conditions that the smoke includes nicotine, the smoke is inhaled in specified concentrations, and the heart is previously damaged in some specified way.

A portion of the disagreement in the literature and in meetings such as this arises from a misunderstanding of which of these two cause-effect concepts is under discussion. A greater disagreement, however, rests on a judgmental decision as to what evidence is necessary to accept either concept.

Epidemiologic Evidence

An extensive literature on associations between smoking and cardiovascular disease is now available. I propose to comment on some of the studies in this literature in which the unit of observation is a person and in which information is collected to characterize persons as to state of health. These are the studies which are commonly referred to as epidemiologic studies. When these studies are interpreted in terms of cause-effect relations the cause-effect concept is usually the pragmatic one.

The proof of cause-effect would be established or rejected by deliberately manipulating the smoking habits of such persons and observing the results. No such studies have been made to my knowledge. Controversy, when it occurs, rests on differences of opinion as to what constitutes proof in the absence of such a manipulative study. There are those who feel that proof is *never* established without such human experimentation. Others feel that proof can be established through observational studies, but there is little agreement as to what sorts of observations are required.

A number of schemes have been suggested for assuring such proof. Koch's postulates are an early attempt, but are applicable only when the causative event is exposure or nonexposure to living organisms. The surgeon general's committee has proposed a number of conditions which must be satisfied. These include consistency, strength, specificity, and coherence of the association. The ultimate decision, however, is said to be judgmental.

In general the acceptability of proof depends on the degree to which observations may be said to mimic the manipulative experiment. Perhaps the best example of such a "natural experiment" is the study that demonstrated a leukemogenic effect of ionizing radiation in the survivors in Hiroshima.

Smoking and Cardiovascular Disease

There is no study of smoking effects which closely resembles this sort of natural experiment. In all available studies persons are characterized as nonsmokers, former smokers, light smokers, heavy smokers, inhalers, and as other descriptive types with respect to the smoking habit. There is no presumption that the assignment to such a category was a chance event, and indeed some investigators have made it clear that the decision to smoke is not a chance event but is to a degree predictable on the basis of characteristics present before the decision is made, on the so-called constitutional characteristics.

We have then associations between smoking and certain cardiovascular diseases that are technically and statistically satisfactory, in the sense that they would rarely occur by chance in our samples if, in fact, smoking had nothing to do with these diseases. We have also associations between certain constitutional factors and smoking, also technically satisfactory. We may think of three possible explanations. First, the constitutional factors may lead to both smoking and disease. Second, smoking may cause disease. Third, disease may cause smoking. These three explanations may all be in effect.

If the constitutional association were a very strong one, so that all or almost all smokers and nonsmokers could be identified by eye color, for example, then we could not support the cause-effect hypothesis. But in fact the constitutional association leaves much room in which to maneuver. We can find, for example, smokers and nonsmokers within both vulnerable and nonvulnerable constitutional types.

When the diseases which are accepted by the committee as causally related are studied it is found that the relative risk is very high, often of the order of 10 to 20. This in essence means that if the cause-effect explanation is correct, it accounts for a very large part of these diseases. For example, it is possible to suppose that most lung cancer may be due to smoking and would be abolished by the cessation of smoking. With the doubtful group, relative risks of the order of 1.5 to

3 are found, and smoking, if causal, can be incriminated in only a small portion of the cases. No one can suppose that the abolition of smoking would wipe out cardiovascular disease or even a very large part of it.

This low relative risk is no argument against the cause-effect hypothesis, but it does make it difficult to give convincing proof of the hypothesis. It opens the possibility that whatever factors cause the majority of these diseases are also responsible for the association with smoking. In the case of lung cancer many of us find it hard to believe that we could have overlooked some confounding variables that are so highly correlated with both smoking and lung cancer. With cardiovascular disease there is the troublesome suspicion that some relatively low-level association really may have been overlooked.

The strongest argument derived from epidemiologic studies in favor of the causal interpretation with respect to coronary disease is the finding that the risk diminishes with time after smoking is abandoned. It should be noted that this by no means decides the debate. It may be hypothesized that the constitutional tendency to smoke also governs the length of time a consumed individual can stay away from the habit. Those who manage to stay away for periods of 5 to 10 years may be supposed to have a low level of constitutional vulnerability to smoking.

As the evidence has accumulated in recent years, the complexity of the hypotheses necessary to contradict the causal hypothesis has increased. It is in evaluating the acceptability of these complex arguments that judgment must play the final role. It is unlikely that all informed scientists will come to the same judgmental decision when studying the same body of data. This will probably dismay many lay people, but it is a phenomenon with which scientists should be familiar. It should not be a cause for despair or distrust among scientists. Finally, it should be possible, as the surgeon general's committee has done, to recognize the point when evidence is adequate to support public health action even though it is not adequate to consider an issue closed.